Formosan Journal of Surgery (2012) 45, 141–145

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.e-fjs.com


ORIGINAL ARTICLE

# Lymphovascular invasion determines the outcome of stage I colorectal cancer patients

**Shih-Ching Chang [a,*], Chun-Chi Lin [a], Huann-Sheng Wang [a], Shung-Haur Yang [a], Jeng-Kai Jiang [a], Yuan-Tzu Lan [a], Tzu-Chen Lin [a], Anna Fen-Yau Li [b], Wei-Shone Chen [a], Jen-Kou Lin [a]**

[a] *Division of Colon & Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan*
[b] *Department of Pathology, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan*

Received 10 April 2012; received in revised form 3 May 2012; accepted 9 June 2012
Available online 4 August 2012

**KEYWORDS**
colorectal cancer;
lymphovascular invasion;
prognosis

**Summary** *Introduction:* The outcome of stage I colorectal cancer (CRC) patients is excellent. However, even after radical surgery, 10% of patients develop tumor recurrence or metastasis.
*Aim:* The aim of this study was to evaluate the prognostic significance of clinicopathologic features to identify high-risk stage I CRC patients.
*Methods:* A total of 292 stage I CRC patients undergoing curative-intention surgery at Taipei Veterans General Hospital between 2000 and 2006 were enrolled. The measured end point was the postoperative disease-free survival (DFS).
*Results:* Of 292 cases, 185 (63.4%) had tumors of T2 stage, 16 (5.5%) had lymphovascular invasion (LVI), and 68 (23.3%) had a carcinoembryonic antigen (CEA) level of higher than 5 ng/mL. With a median follow-up period of 60 months (range, 6–130 months), CRC recurred in 23 patients. Overall, 5-year DFS was 88.7% in stage I disease patients. In the univariate analysis, 5-year DFS of patients with LVI was 52.7%, which was significantly poorer than that of patients without LVI (90.9%). Patients with a high CEA level or T2 lesion had a poor 5-year DFS, but the difference did not reach statistical significance. In the multivariate analysis, the only important independent factor affecting the 5-year DFS was LVI (hazard ratio = 4.27; 95% confidence interval: 1.88–9.68; $p = 0.001$). In the T1 disease, 5-year DFS of patients with LVI was 60.0%, significantly poorer than that of patients without LVI (93.4%; $p = 0.045$). In the T2 disease, the difference of 5-year DFS between patients with and without LVI was more significant (50.5% vs. 85.1%; $p = 0.003$).

* Corresponding author. Division of Colon & Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital, National Yang-Ming University, Taipei 112, Taiwan.
*E-mail address:* changsc@vghtpe.gov.tw (S.-C. Chang).


http://dx.doi.org/10.1016/j.fjs.2012.06.006

*Conclusion:* Stage I CRC patients in this study had an excellent outcome. Prognosis of patients having tumor with LVI was poor and should receive an aggressive follow-up protocol.


## 1. Introduction

In Taiwan, colorectal cancer (CRC) is the most common form of cancer and the third leading cause of cancer death. At present, more than 10,000 new cases of colonic cancer are diagnosed yearly.[1] Approximately 20% of patients will have stage I colon cancer (T1-2N0M0) at the time of diagnosis.[2,3]

There is no doubt that the majority of stage I colon cancer patients are indeed cured by surgery alone. Also, the present National Comprehensive Cancer Network (NCCN) guideline does not recommend the use of adjuvant chemotherapy for patients with stage I lesions.[4] In the recommendation of post-treatment surveillance, follow-ups for patients with stage I disease need not be as frequent as that for patients with stage II or III disease.[4] Although the prognosis of stage I disease patients is excellent, about 10% of patients will develop local relapse and metastatic disease despite an R0 resection.[5] Subgroups with high-risk characteristics for tumor recurrence should be identified to receive an aggressive follow-up surveillance.

In this study, we found that lymphovascular invasion (LVI) was an independent prognostic factor of stage I disease patients. Stage I disease patients with LVI should receive an aggressive follow-up protocol.

## 2. Materials and methods

### 2.1. Patients and clinical findings

A total of 351 stage I CRC patients who underwent surgery at Taipei Veterans General Hospital from 2000 to 2006 were initially screened for enrollment in this study. Prior to surgery, several surveillance procedures were performed, including colonoscopy and computed tomography (CT) scans of the area from the neck to the pelvis. First of all, 13 patients who received preoperative chemoradiotherapy were excluded from this study. For patients with symptomatic bone pain or high carcinoembryonic antigen (CEA) levels, whole-body bone scans were performed. All clinical findings were recorded in detail prospectively and were stored in computerized files. The database included the following information: (1) name, gender, age, family history, and major medical problems; (2) location, size, gross appearance, stage, differentiation, and important pathological prognostic features of the tumor; and (3) type of operation, complications, recurrence, and follow-up conditions. The disease stage was determined according to the Tumor-Node-Metastasis (TNM) classification system of the American Joint Committee on Cancer.[6,7] Important pathological features of the tumors were defined according to the consensus statement of the College of American Pathologists[6] and included LVI, and differentiation. After surgery, patients were monitored every 3 months for the first 2 years and every 6 months thereafter. At each visit, imaging studies, including chest radiography and either abdominal ultrasonography or abdominopelvic CT, were performed. Colonoscopy was performed every 6 months to 1 year after surgery and every 3 years thereafter. Unscheduled CT, a whole-body bone scan, or positron emission tomography was performed for patients with increased serum levels of CEA or CA19-9 or for symptomatic patients. Our definition of high-risk factors originated from the NCCN guidelines,[4] including emergency surgery, lymphovascular involvement, poorly differentiated histology, lymph nodes harvested less than 12 in number, and a high CEA level. Finally, 46 patients were dropped out from this study, including 24 (7.1%) patients without any follow-up records, 15 (4.4%) patients whose pathologic records showed only TNM staging but no microscopic descriptions, and seven (2.1%) patients without any CEA levels. Therefore, in total 292 cases were enrolled for the statistical analysis.

## 3. Statistical analysis

The statistical end point of the analyses was the disease-free survival (DFS) from the date of surgery. Group distributions for each clinicopathologic trait were compared using two-tailed Fisher's exact procedure and the chi-square test. Numerical values were compared using Student $t$ test. Data are expressed as mean $\pm$ standard deviation. Kaplan–Meier survival curves were plotted and compared using the log-rank test. A multivariate analysis was performed using the Cox proportional hazard model. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS for Windows version 13.0 software.

## 4. Results

A total of 292 stage I CRC patients undergoing curative-intention surgery were enrolled in this study. The patient population was composed of 184 men (63.0%) and 108 women (37.0%). The mean age at tumor resection was 63.1 $\pm$ 10.3 years (range, 22–86 years; median, 64 years). As regards tumor locations, 159 (54.6%) were colonic and 133 (45.4%) were rectal. The mean lymph node number harvested was 14.5 $\pm$ 8.2 (range, 0–56; median, 12). In 116 cases (39.7%), less than 12 lymph nodes were harvested.

In these 292 cases, 185 (63.4%) had tumors of T2 stage, 16 (5.5%) had LVI, and 68 (23.3%) had a CEA level higher than 5 ng/mL, and three tumors were poorly

differentiated. Twenty-one (7.2%) patients had mucinous adenocarcinoma and 52 (17.8%) had infiltrative lymphocytes in the tumors. No perineural invasion was found in our series. Only one received emergency operation due to obstruction. Since the number of cases having emergency operation and poor differentiation of the tumor was small, these two factors were excluded in the statistical analysis.

With a median follow-up period of 60 months (range, 6–130 months), CRC recurred in 23 patients (14 cases of liver metastasis, 10 cases of lung metastasis, and 3 cases of peritoneal carcinomatosis). Overall, the 5-year DFS was 88.7% in stage I disease patients.

According to a univariate analysis, only LVI affected 5-year DFS of stage I disease patients significantly. As shown in Table 1, the 5-year DFS of patients with LVI was 52.7%, which was significantly poorer than that of patients without LVI (90.9%). Patients with a high CEA level or T2 lesion had a poor 5-year DFS, but the difference did not reach statistical significance. In the multivariate analysis (Table 2), the only important independent factor affecting the 5-year DFS was LVI [hazard ratio (HR) = 4.27; 95% confidence interval (CI): 1.88–9.68; $p = 0.001$]. Of 107 patients with T1 tumors, five (4.7%) had LVI. Eleven patients with T2 tumors (5.9%) had LVI. As shown in Fig. 1, in the T1 disease, the 5-year DFS of patients with LVI was 60.0%, significantly poorer than that of patients without LVI (93.4%; $p = 0.045$). In the T2 disease, the difference of 5-year DFS between patients with and without LVI was more significant (50.5% vs. 85.1%; $p = 0.003$).

**Table 1** Univariate analysis for 5-year DFS.

| Variable | No. | 5-year DFS (%) | $p$[a] |
|---|---|---|---|
| Age (y) | | | |
| >70 | 131 | 87.5 | 0.212 |
| <70 | 161 | 89.7 | |
| Gender | | | |
| Male | 184 | 88.4 | 0.327 |
| Female | 108 | 89.5 | |
| Tumor location | | | |
| Colon | 159 | 89.2 | 0.603 |
| Rectum | 133 | 88.4 | |
| Tumor depth | | | |
| T1 | 107 | 91.3 | 0.085 |
| T2 | 185 | 83.0 | |
| Preoperative CEA level (ng/mL) | | | |
| <5 | 224 | 90.2 | 0.119 |
| >5 | 68 | 79.0 | |
| Lymphovascular invasion | | | |
| No | 276 | 90.9 | 0.001 |
| Yes | 16 | 52.7 | |
| Mucinous adenocarcinoma | | | |
| No | 271 | 89.5 | 0.076 |
| Yes | 21 | 79.3 | |
| Tumor infiltrative lymphocyte | | | |
| Yes | 52 | 90.2 | 0.353 |
| No | 240 | 87.8 | |
| Tumor border | | | |
| Expansive | 141 | 89.2 | 0.393 |
| Infiltrative | 151 | 87.3 | |
| Lymph node harvested | | | |
| >12 | 176 | 89.2 | 0.715 |
| <12 | 116 | 87.8 | |

CEA = carcinoembryonic antigen; DFS = disease-free survival.
[a] Log-rank test.

**Table 2** Multivariate analysis for 5-year DFS.

| Factor | 5-year DFS | | |
|---|---|---|---|
| | HR | 95% CI | $p$ |
| Tumor depth | | | |
| T2 vs. T1 | 1.83 | 0.88–3.79 | 0.106 |
| Preoperative CEA level (ng/mL) | | | |
| >5 vs. <5 | 1.49 | 0.76–2.88 | 0.243 |
| Lymphovascular invasion | | | |
| Yes vs. no | 4.27 | 1.88–9.68 | 0.001 |
| Mucinous adenocarcinoma | | | |
| Yes vs. no | 2.27 | 0.92–3.21 | 0.074 |
| Tumor infiltrative lymphocyte | | | |
| No vs. yes | 1.27 | 0.28–1.93 | 0.532 |
| Tumor border | | | |
| Infiltrative vs. expansive | 1.25 | 0.47–1.78 | 0.921 |
| Tumor location | | | |
| Rectum vs. colon | 1.14 | 0.61–2.41 | 0.683 |
| LN harvested | | | |
| <12 vs. >12 | 1.24 | 0.65–2.35 | 0.508 |

The $p$ value results from the hypothesis that the HR (as determined by multivariate binary logistic regression analysis) is 1.0. CEA = carcinoembryonic antigen; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; LN = lymph node.

## 5. Discussion

Patients with stage I CRC have an excellent prognosis after oncologic resection, with reported 5-year survival rates of about 90%.[8,9] Our results showed that 5-year DFS of stage I CRC patients was 88.7%, which was compatible with the results of previous studies.[5,8,9]

Based on the evidence from multiple statistically robust published trials and the fact that these are generally used in patient management, tumor depth, LVI, and the CEA level can be classified as Category I prognosticators. However, we identified only LVI as the independent prognostic factor of the outcome of stage I CRC patients. For stage I disease, the cause of tumor recurrence or metastasis must be an undetected or undetectable local or systemic residual of the tumor at operation. Evidence has emerged showing a significant amount of nodal metastases of 2 mm or less, likely to be missed during conventional gross pathological specimen examination.[5,10,11] Tumors

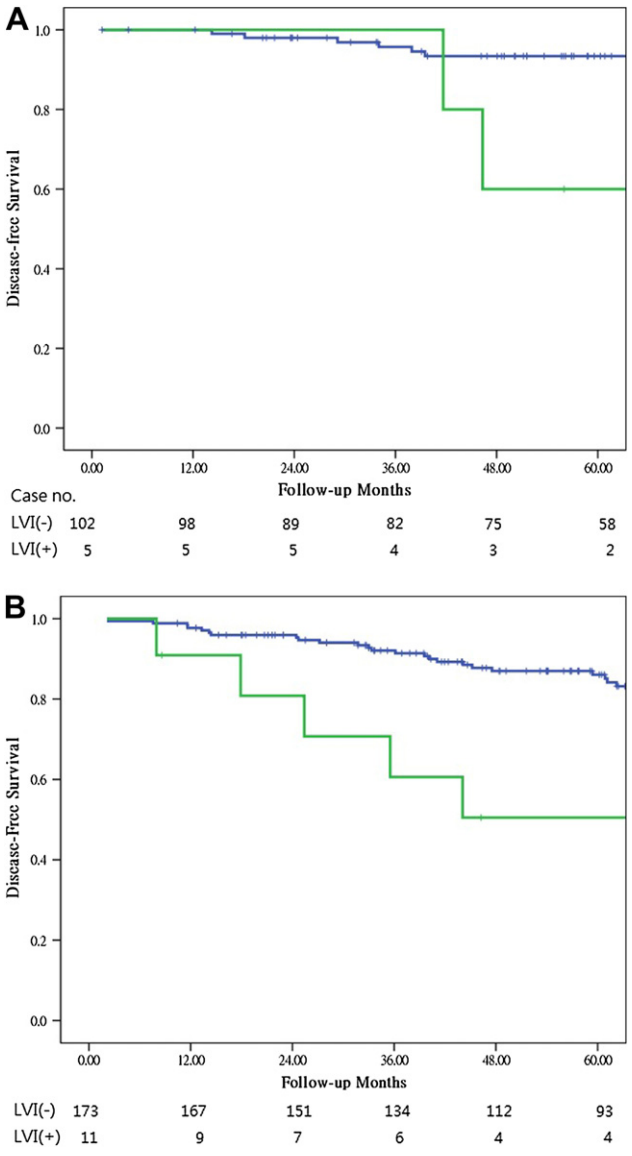


**Figure 1** The 5-year DFS rate according to status of LVI (blue line: without LVI; green line: with LVI). (A) In the T1 disease, the 5-year DFS in patients with and without LVI was 60.0% and 93.4%, respectively. (B) In the T2 disease, the 5-year DFS in patients with and without LVI was 50.5% and 85.1%, respectively. DFS = disease-free survival; LVI = lymphovascular invasion.

with LVI might be an indicator of occult or undetectable metastasis. In a previous study, immunohistochemical assessment showed that LVI was associated with the presence of micrometastasis in patients with N0 stage.[12] Also, several studies demonstrated that in T1 or T2 CRC, LVI was the independent predictor of lymph node metastases, as shown by multivariate analysis.[13–15] Recently, a prospective study demonstrated that primary colon cancer with extension to the muscularis propria or beyond, LVI, or high tumor grade correlated with occult metastases in regional lymph nodes. The possible progression steps are now established, and LVI plays an important role in the formation of occult metastasis.[15] However, the recent NCCN guideline did not suggest that such stage I CRC patients should receive chemotherapy. Since the prognosis of stage I CRC patients with LVI is poor, an aggressive follow-up should be recommended in such patients.[4]

Although in our study there was a trend showing that patients with a T2 lesion or high CEA level had a poor outcome in the stage I disease, the difference was not significant. The possible explanation appears to be the small sample size. To achieve statistical significance supporting the T2 lesion or high CEA level as a prognostic factor for patients with stage I disease, the estimated minimum sample size should probably be 1000 or above. The recent nationwide study from Germany demonstrated that the impact of the T2 stage is twice that of the T1 stage for colorectal patients.[16]

For stage II diseases, several professional organizations have proposed a minimum node yield of 12 to allow accurate staging.[17,18] For stage I disease, recent analysis of pathological staging from the SEER database suggested that at least four lymph nodes should be harvested to achieve a probability of correct staging of 90%.[19] In our study, the mean number of lymph nodes harvested in T1 and T2 disease was 12.3 ± 8.6 and 15.2 ± 10.3, respectively.In about 40% and 7% of cases, the number of lymph nodes harvested was less than 12 and 4, respectively. However, the outcome of these patients was similar to those who had a higher lymph node harvest with a cutoff value of either 12 or 4 lymph nodes. The number 12 or 4 probably does not hold any particular biological significance. The true effect of lymphadenectomy remains debated, as does the minimum number of nodes necessary for an adequate resection.[20–23] The possible benefit might be more likelihood of actually identifying stage III disease patients or possibly decreasing local recurrence by resection of affected lymph nodes.

Although our database was made prospectively, the study design has limitations associated with its retrospective nature. About 15% of patients with incomplete data dropped out from the database. We do not know whether the inclusion of these cases would have had influenced the patient outcome statistics. Furthermore, the proportion of the LVI in stage I disease was only about 6%. We could not conclude whether stage I CRC patients with LVI should receive chemotherapy or not.

In conclusion, the stage I CRC patients have an excellent outcome. However, the prognosis of patients having LVI is poor and the patients should receive an aggressive follow-up protocol.

## References

1. The Department of Health, the Executive Yuan, Taiwan, R.O.C. *Cancer Registry Annual Report*. December 2007.
2. Jessup JM, Menck HR, Steele Jr GD, Menck HR, Winchester DP. The National Cancer Data Base. Report on colon cancer. *Cancer*. 1996;78:918–926.
3. Ju JH, Chang SC, Wang HS, et al. Changes in disease pattern and treatment outcome of colorectal cancer: a review of 5,474 cases in 20 years. *Int J Colorectal Dis*. 2007;22:855–862.
4. Engstrom PF, Arnoletti JP, Benson III AB, et al. National Comprehensive Cancer Network. NCCN clinical practice

guidelines in oncology: colon cancer. *J Natl Compr Canc Netw*. 2009;7:778—831.
5. Iddings D, Ahmad A, Elashoff D, Bilchik A. The prognostic effect of micrometastases in previously staged lymph node negative (N0) colorectal carcinoma: a meta-analysis. *Ann Surg Oncol*. 2006;13:1386—1392.
6. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med*. 2000;124:979—994.
7. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010:113—120.
8. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst*. 2004;96:1420—1425.
9. Nicastri DG, Doucette JT, Godfrey TE, Hughes SJ. Is occult lymph node disease in colorectal cancer patients clinically significant? A review of the relevant literature. *J Mol Diagn*. 2007;9:563—571.
10. Bilchik A, Nissan A, Wainberg Z, et al. Surgical quality and nodal ultrastaging is associated with long-term disease-free survival in early colorectal cancer: an analysis of 2 international multicenter prospective trials. *Ann Surg*. 2010;252:467—474.
11. Mescoli C, Rugge M, Pucciarelli S, et al. High prevalence of isolated tumor cells in regional lymph nodes from pN0 colorectal cancer. *J Clin Pathol*. 2006;59:870—874.
12. Okabe S, Shia J, Nash G, et al. Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. *J Gastrointest Surg*. 2004;8:1032—1039.
13. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum*. 2002;45:200—206.
14. Chok KS, Law WL. Prognostic factors affecting survival and recurrence of patients with pT1 and pT2 colorectal cancer. *World J Surg*. 2007;31:1485—1490.
15. Wasif N, Faries MB, Saha S, et al. Predictors of occult nodal metastasis in colon cancer: results from a prospective multicenter trial. *Surgery*. 2010;147:352357.
16. Mroczkowski P, Schmidt U, Sahm M, Gastinger I, Lippert H, Kube R. Prognostic factors assessed for 15,096 patients with colon cancer in stages I and II. *World J Surg*. 2012;36:1693—1698.
17. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst*. 2001;93:583—596.
18. Schofield JB, Mounter NA, Mallett R, Haboubi NY. The importance of accurate pathological assessment of lymph node involvement in colorectal cancer. *Colorectal Dis*. 2006;8:460—470.
19. Gonen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. *J Clin Oncol*. 2009;27:6166—6171.
20. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA. Lymph node evaluation in colorectal cancer patients: a population-based study. *J Natl Cancer Inst*. 2005;97:219—225.
21. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst*. 2007;99:433—441.
22. Berger AC, Watson JC, Ross EA, Hoffman JP. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am Surg*. 2004;70:235—240.
23. Bui L, Rempel E, Reeson D, Simunovic M. Lymph node counts, rates of positive lymph nodes, and patient survival for colon cancer surgery in Ontario, Canada: a population-based study. *J Surg Oncol*. 2006;93:439—445.